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Short Communication

Immunometabolic Interactions in Pancreatic Disease: Crosstalk Between Energy Dysregulation, Immune Activation, and Tissue Dysfunction

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DESCRIPTION

Pancreatic disorders arise from a complex interaction between metabolic imbalance and immune system activation, where disturbances in energy handling and inflammatory signaling reinforce one another. This combined field of immunometabolism examines how nutrient processing, cellular energy pathways, and immune responses influence each other within pancreatic tissue. In healthy physiology, the pancreas maintains tight coordination between metabolic demand and immune surveillance, ensuring stable enzyme production and hormonal regulation. However, in disease states, this balance becomes disrupted, leading to progressive tissue injury, functional decline, and systemic effects [1].

The pancreas is highly sensitive to metabolic fluctuations due to its dual role in digestion and endocrine regulation. Acinar cells require substantial energy to synthesize and secrete digestive enzymes, while endocrine cells regulate glucose levels through hormone secretion. These activities depend on efficient mitochondrial function and regulated substrate availability [2]. When metabolic stress occurs, cellular energy deficits can impair both enzyme production and hormone release, creating vulnerability to immune-mediated damage.

Immune activation within the pancreas is triggered by cellular injury, microbial signals, and metabolic stress signals. Damaged pancreatic cells release danger-associated molecular patterns that activate resident immune cells. These signals initiate inflammatory cascades that recruit additional immune populations from circulation. While this response is intended to limit injury and promote repair, excessive or prolonged activation leads to tissue damage and functional impairment [3].

Mitochondrial dysfunction is a central feature of immunometabolic imbalance in pancreatic disease. Mitochondria regulate both energy production and inflammatory signaling. When mitochondrial efficiency declines, reactive oxygen species accumulate and contribute to cellular stress. These molecules not only damage cellular components but also act as signaling mediators that amplify immune activation. Adipose tissue surrounding the pancreas also contributes to immunometabolic interactions. Fat accumulation in and around pancreatic tissue can release inflammatory mediators that influence local immune activity. This ectopic fat deposition is associated with increased tissue inflammation and reduced functional capacity of both exocrine and endocrine compartments [4].

Endocrine dysfunction significantly affects immune regulation within pancreatic disease. Insulin not only regulates glucose metabolism but also has modulatory effects on immune cell activity. Reduced insulin signaling can therefore contribute to enhanced inflammatory responses. Conversely, inflammatory mediators can impair insulin secretion, creating a bidirectional relationship between metabolic and immune pathways. Glucagon and somatostatin also influence immunometabolic balance. These hormones regulate energy availability and digestive activity, indirectly affecting immune cell behavior. Disruption of hormonal signaling can therefore contribute to systemic metabolic instability and altered immune responses [5].

Gut-derived metabolic signals further influence pancreatic immunometabolism. Nutrients, microbial metabolites, and intestinal hormones enter systemic circulation and interact with pancreatic tissue. Changes in gut metabolism can alter immune activity within the pancreas, highlighting the interconnected nature of digestive and metabolic systems. Dysbiosis of the intestinal microbiota contributes to immunometabolic imbalance by producing metabolites that influence inflammation and energy metabolism. Certain microbial byproducts enhance inflammatory signaling, while others support metabolic stability. Shifts in microbial composition can therefore have significant effects on pancreatic immune activity [6].

Fibrosis itself contributes to metabolic dysfunction by reducing oxygen delivery and limiting nutrient exchange within pancreatic tissue [7]. This structural change creates hypoxic conditions that further impair mitochondrial function and promote inflammatory signaling. The interaction between fibrosis and immunometabolic imbalance creates a self-reinforcing cycle of disease progression. Vascular dysfunction plays a significant role in pancreatic immunometabolism. Reduced blood flow limits

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nutrient delivery and impairs immune cell regulation. Endothelial dysfunction can also enhance inflammatory signaling and promote leukocyte adhesion, further amplifying immune responses within pancreatic tissue [8].

Autophagy, a cellular process responsible for recycling damaged components, is closely linked to immunometabolic regulation. When autophagy is impaired, damaged mitochondria and misfolded proteins accumulate, increasing cellular stress and immune activation. Proper autophagic function is therefore essential for maintaining metabolic and immune balance [9]. Nutrient excess, particularly high lipid intake, contributes to immunometabolic disruption. Excess fatty acids can activate inflammatory pathways and impair mitochondrial function. This leads to increased oxidative stress and further immune activation within pancreatic tissue.

Conversely, nutrient deficiency can also impair immunometabolic balance. Insufficient energy supply limits cellular repair mechanisms and reduces the ability of pancreatic cells to respond to stress. Both excess and deficiency of nutrients can therefore contribute to disease progression. Genetic predisposition influences individual susceptibility to immunometabolic imbalance [10]. Variations in genes regulating inflammation, mitochondrial function, and metabolic pathways can alter disease progression. These genetic differences contribute to variability in clinical outcomes among patients with similar environmental exposures.

CONCLUSION

Immunometabolic interactions play a central role in pancreatic disease development and progression. The interplay between metabolic dysfunction and immune activation creates a dynamic environment that drives tissue injury and functional decline. Immune cell populations within pancreatic tissue exhibit functional diversity that influences disease progression. Some immune cells promote inflammation, while others support tissue repair. The balance between these populations determines whether tissue damage progresses or stabilizes.Understanding these interactions provides important insight into disease mechanisms and offers potential pathways for therapeutic intervention aimed at restoring balance within pancreatic tissue.

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